REMARKS

Claims 1-3, 5-10, and 12-15 are of record in this application. Claims 1, 8, 9, and 15 have been amended, and claims 4 and 11 have been canceled. No new claims have been added.

Support for the amendments to the claims is inherent in the original disclosure. Claims 1, 9, and 15 have all been amended to insert the limitation of claim 4 (or 11) therein. Support for the recitation in claims 8 and 9 that the viral agent is present in an amount effective to elicit "a protective" immune response may be found at lines 5-20 of paragraph no. 0063, on page 18 of the specification.

Rejection Under 35 U.S.C. 112

Claims 3, 5, 10, and 12 have been rejected under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure. The Examiner has indicated that a deposit of the claimed recombinant virus does not indicate the extent of public availability.

In response, the disclosed and claimed recombinant Marek's disease virus clone CVRM-2 was deposited under the provisions of the Budapest Treaty in the American Type Culture Collection

(ATCC), 10801 University Blvd., Manassass, Virginia 20110-2209, USA, on January 22, 2003, and was assigned Accession No. ATCC PTA-4945.

Applicants' representative, Randall E. Deck, further states that in addition to the deposit meeting the terms of the Budapest Treaty:

(1) all restrictions on the availability of the deposit will be irrevocably removed upon the granting of the patent, and

(2) the deposit will be replaced if it should become non-viable.

Rejection Under 35 U.S.C. 112

Claims 3 and 8-13 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Each of the issues raised by the Examiner are addressed hereinbelow.

A. Claims 3 and 10 have been rejected as indefinite in reciting the use of a *PacI* excised fragment. The Examiner has indicated that the identity of the particular restriction site would appear to be irrelevant, especially since the site would be lost during recombination. Applicants respectfully disagree.

It may be that *PacI* sites from the original RM1 fragment (containing the claimed LTR) may be lost during excision from the RM1 genome. However, these sites would most likely be present in the recipient CVI988 MDV strain (or any other CVI988 strain) because the herpesvirus genome is highly conserved. Thus, the resultant recombinant having the LTR's inserted therein should also have functional *PacI* sites present. The LTR's could be excised from these recombinants by *PacI* digestion. Moreover, as disclosed in paragraph no. 0057 on page 15 of the specification, the presence of the *PacI* restriction sites allows the LTRs to be inserted into any desired CVI988/X strain. A DNA fragment containing the inserted LTRs may be excised from the deposited CVRM-2 strain, and subsequently used to transform any CVI988/X strain.

B. Claims 8 and 9 have been rejected as indefinite in reciting that the vaccine elicits an "immune response" rather than a "protective immune response". Applicants respectfully disagree.

Although the Examiner's point is well taken, Applicants believe that the limitation was implicit in the original claims in view of the definition of an effective immunization dosage in paragraph no. 0063 on page 18 of the specification, and, in the

case of claim 9, in view of the preamble. However, the claim has been amended as suggested by the Examiner in an effort to expedite prosecution.

Rejections Over the Prior Art

Applicants note that the Examiner has not specifically included claims 3 and 10 in the 35 U.S.C. 103 rejections for the reasons set forth on page 4, paragraph 2, of the Office action. Moreover, Applicants note that it appears that claims 7 and 12 are to be included in the §103 rejection over the two Witter publications. Although these claims are not listed in the initial paragraph of the rejection they are referred to in paragraph 3 on page 7 of the Office action.

However, the status of claims 8, 14, and 15 is not clear. These claims were not included in either prior art rejection. It is not clear if these claims have been deemed free of the prior art or if they are not patentable over the prior art. Clarification is requested.

Rejection Under 35 U.S.C. 103

Claims 1, 2, 5-7, 9, 12, and 13 have been rejected under 35 U.S.C. 103 as being unpatentable over Witter *et al.* (1997) in

view of Witter *et al.* (1995). The Examiner has taken the position that it would have been obvious to substitute the CVI988/Rispens strain of Witter *et al.* (1995) for the JM/102W strain of Witter *et al.* (1997). Applicants respectfully disagree.

Witter *et al.* (1997, hereinafter referred to as Witter '97) disclosed a recombinant Marek's disease virus, referred to as RM1, which had the long terminal repeats (LTRs) of a reticuloendotheliosis virus (REV) stably integrated into the repeat short (RS) regions of its genome. This strain was generated at the USDA-ARS-ADOL from a pathogenic serotype 1 Marek's disease virus, strain JM/102W, after co-cultivation with REV. Although the RM1 strain was shown to provide a level of protection similar or superior to that of CVI988, it was also associated with residual pathogenicity, and caused thymic atrophy in treated birds. The authors noted that the reason why the RM1 strain possessed these properties "cannot be definitively established" and speculated that there were several possible mechanisms for the activity of the RM1 strain, including the "possibility" that the insertion of the REV sequences caused a specific mutation in the Marek's disease virus genome (page 418,

third paragraph). The authors concluded that the RM1 may provide a model for future vaccines, stating that:

> "If the superior protection by RM1 clones derives from the selective attenuation of oncogenicity without influence on *in vivo* replication or other properties, then perhaps selective mutation of key genes will prove to be a useful strategy for developing superior serotype 1 vaccines" (emphasis added, see the paragraph bridging pages 419-420).

Witter *et al.* (1995, hereinafter referred to as Witter '95) disclosed the characteristics of two Marek's disease virus strains, CVI988/Rispens and R2/R3. The CVI988/Rispens strain was disclosed to provide improved disease protection with a reasonable degree of safety.

The instant invention is drawn to Applicants' discovery that an effective vaccine for Marek's disease may be prepared using a recombinant Marek's disease virus strain CVI988 transformed with a foreign DNA construct which includes a long terminal repeat sequence (LTR) of a reticuloendotheliosis virus. This viral agent is effective to elicit a protective immune response in a chicken to Marek's disease virus without causing a significant degree of pathogenicity in the inoculated bird. Recombinant Marek's disease viruses having the LTRs integrated into their genome replicated faster than the parental CVI988 strain and were recovered and isolated. Applicants believe that this increased rate of replication is the result of the insertion of the

reticuloendotheliosis virus LTR into the genome of the Marek's disease virus upstream of the ICP4 gene (see the specification at page 14, paragraph no. 0055, last 5 lines). This is not disclosed or suggested in the prior art.

It is well established that the prior art must provide at least some predictability or a reasonable expectation of success to render a claimed invention obvious. See *In re Whiton* (CCPA 1970) 164 USPQ 455, *In re Rinehart* (CCPA 1976) 189 USPQ 143, and *In re Longhi* (CAFC 1985) 225 USPQ 645.

In the instant fact situation, although Witter '97 recognized the RM1 mutant virus provided a high level of protection against infection with Marek's disease virus, the authors readily admitted that the reason or mechanism for the increase in protection was unknown. It was not known if the effect was reproducible in other Marek's disease virus strains. Specifically, Witter '97 only suggested that "If the superior protection...derives from the selective attenuation of oncogenicity without influence on *in vivo* replication or other properties, then perhaps selective mutation of key genes will provide a useful strategy for development of superior serotype 1 vaccines" (emphasis added). Thus, there is no reasonable expectation of success.

The production of this single RM1 strain in Witter '97 is insufficient to establish any pattern or predictability linking the introduction of the LTRs into other Marek's disease virus strains, with increased vaccine efficacy. In other words, simply because one Marek's disease virus strain which has LTRs inserted into its genome exhibits increased efficacy, does not imply or suggest that all Marek's disease viruses transformed with LTRs will do the same. This is even more apparent considering the express acknowledgment by the primary reference that the result is uncertain.

At best, the prior art would only suggest that it would be obvious to try the substitution suggested by the Examiner. However, it is also well known that a rejection of obviousness under 35 U.S.C. 103 must be based on more than just a suggestion that it would be "obvious to try".

In addition to the comments above, Applicants submit that even if the prior art provided the motivation to try to repeat the process of Witter '97 using another MDV such as CVI988, it would be highly unlikely that the process could be successfully repeated without the benefit of Applicant's invention. As disclosed in the specification at paragraph 0055 and recited in

the amended claims, to be effective, the LTRs should be inserted upstream of the ICP4 gene of the Marek's disease virus. However, if a practitioner of ordinary skill in the art were to attempt to repeat the process of Witter '97 using a different Marek's disease virus strain, the LTRs could be inserted at numerous locations in the genome of the virus. This point of insertion would vary and could not be controlled. The skilled practitioner would have no reasonable expectation of success that the LTRs would be inserted at the correct position. It is only by virtue of Applicants' invention that the point of insertion can be controlled and LTRs can be introduced into other Marek's disease viruses to produce effective vaccines.

The other reference relied upon, Witter '95, does nothing to compensate for the deficiencies of Witter '97. The reference merely discloses the desirable properties of the CVI988/Rispens vaccine strain. It does not disclose or suggest inserting LTRs into the genome of CVI988, much less provide any guidance how that may be effected.

The unpredictability of repeating the process of Witter '97 using other virus strains is even more apparent in view of the disclosure of Parcells *et al.* [2004, Insertion of the LTR from reticuloendotheliosis virus (REV) upstream of SORF2 does not

necessarily confer the phenotype associated with the RM1 strain of MDV, Abstract presented at the 7th International Marek's Disease Symposium, July 10-14, 2004, St. Catherine's College, Oxford, UK, a copy of which is enclosed herewith]. In brief, the authors attempted to do just what the Examiner has suggested: to insert the LTRs into the genome of Marek's disease virus strain CVI-988 at the same location that the LTRs were inserted into the RM1 strain (the same as that reported by Witter '97). However, despite their efforts, the authors reported that the resultant transformants containing the inserted LTRs did not exhibit enhanced replication. This failure clearly demonstrates that there would be no predictability or reasonable expectation of success in repeating the process of Witter '97 as suggested by the Examiner.

Applicants note that the above-mentioned Parcells abstract was presented in July, 2004, nearly one year after the filing date of the instant application, and therefore does not qualify as prior art under 35 U.S.C. 102.

Rejection Under 35 U.S.C. 103

Claims 4 and 11 have been rejected under 35 U.S.C. 103 as being unpatentable over Witter *et al.* (1997) in view of Witter *et*

al. (1995), as applied to claims 1 and 9, further in view of Jones *et al.* (1996). The Examiner has taken the position that Jones discloses the point of insertion of the LTRs. Applicants respectfully disagree.

Jones *et al.* (1996, hereinafter referred to as Jones '96) further characterizes the properties of the RM1 strain referred to in Witter '97, and discloses that the LTRs are inserted upstream of the ICP4 gene.

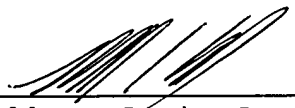
Although Jones '97 discloses the location of the LTR's insertion and its relation to the ICP4 gene, the reference does nothing to correct for the deficiencies of the primary reference. The claims are still not obvious for the same reasons presented in the response to the §103 rejection of claims 1 and 9, *supra*. As Applicants have demonstrated above, a practitioner of ordinary skill in the art would still have no motivation to combine the references as suggested, nor would they have any reasonable expectation of success.

A copy of the Parcells *et al.* abstract cited hereinabove is enclosed. It has <u>not</u> been supplied with an Information Disclosure Statement (with its accompanying fees) or listed on a form PTO-1449 because it does not: (1) establish a prima facie

case of unpatentability, or (2) refute any position taken by applicants, as defined by 37 CFR 1.56(b).

For the reasons stated above, claims 1-3, 5-10, and 12-15 are believed to satisfy the requirements of 35 U.S.C. 103 and distinguish over the prior art of record. Allowance thereof is respectfully requested.

Respectfully submitted,



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Enclosures:
-Parcells *et al.* [2004, Insertion of the LTR from reticuloendotheliosis virus (REV) upstream of SORF2 does not necessarily confer the phenotype associated with the RM1 strain of MDV, Abstract presented at the 7th International Marek's Disease Symposium, July 10-14, 2004, St. Catherine's College, Oxford, UK, 2 pages]

PLENARY SESSION III
Virulence and Virus Evolution

III.2

Insertion of the LTR from reticuloendotheliosis virus (REV) upstream of SORF2 does not necessarily confer the phenotype associated with the RM1 strain of MDV

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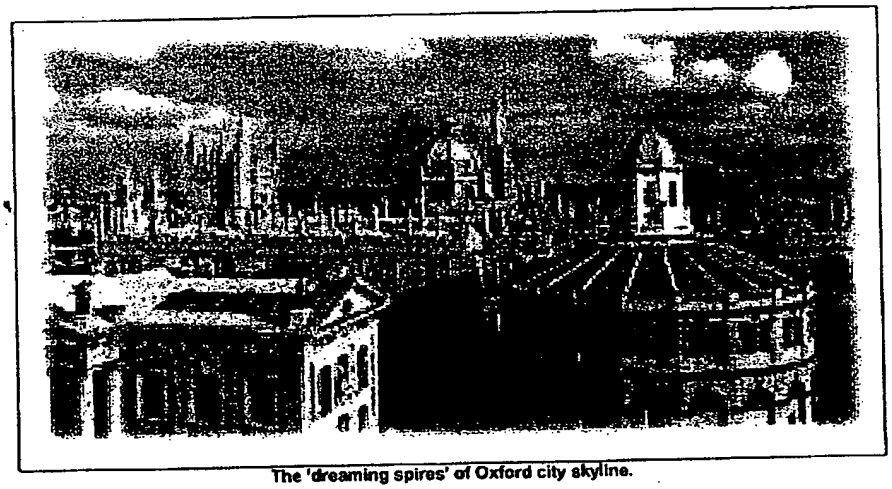
The insertional mutagenesis of the MDV genome by retroviruses (ALV, REV) has provided unique insight into a possible mechanism of herpesvirus evolution. The isolation of the RM1 virus, from a highly-attenuated strain of MDV (JM-102) passaged with reticuloendotheliosis virus (REV) chicken syncytial virus (CSV) and found to have enhanced replication *in vivo*, was very supportive of this concept. Characterization of RM1, which contained an insertion of a truncated LTR within the repeats flanking the unique short region (IRs and TRs), showed an increased level of transcription across the SORF2 gene. As RM1, unlike JM-102 at similar passage level, induced thymic atrophy, was non-oncogenic when inoculated into one day-old chickens and provided complete protection against vv+MDV, there was a strong correlation of the LTR insertion and this phenotype. To replicate this finding and determine if this insertion alone could confer enhanced replication of MDV, a vaccine strain (CVI-988) was sequentially constructed to contain the insertion of the LTR sequence from RM1 at the identical location within the IRs. This recombinant MDV was constructed via incorporation of the LTR adjacent to a loxP site-flanked GFP expression cassette (loxP-CMV-lacsmGFP-polyA-loxP). Recombinant MDVs were screened according to GFP expression and the isolated recombinant DNA was treated with Cre recombinase *in vitro*. Non-fluorescent MDVs were then isolated and plaque purified. We were able to generate both GFP+ and GFP- viruses containing the LTR from RM1 inserted in either orientation at the specific locus. Interestingly, no dual insertions were noted in stocks of these viruses and the recombinants contained insertions in only the IRs, but not the TRs region of the genomes. Characterization of the parental, GFP+ and GFP- viruses showed that the recombinants did not replicate *in vivo* to the same level as the parent virus. Stocks of the viruses reisolated from birds showed that the A orientation recombinants (same LTR orientation as RM1) were stable after *in vivo* replication, yet the GFP- B orientation recombinant was not. In no instance was duplication of the insertion at both repeats noted. The inability of the RM1-like LTR insertion in a CVI-988 background to confer enhanced replication *in vivo* may be due to slight differences of the insert sequence (Lox site), or insertion in only one of the two inverted repeats. Mutations other than the LTR insertion within the IRs/TRs may also contribute to the enhanced replication of RM1.

Notes:

7th International Marek's Disease Symposium

2004

Abstract book



The 'dreaming spires' of Oxford city skyline.

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